BRITISH MEDICAL JOURNAL

LONDON SATURDAY MAY 7 1949

PATHOGENESIS OF ESSENTIAL HYPERTENSION*

BY

F. H. SMIRK, M.D., Ch.B., F.R.C.P., F.R.A.C.P.

Professor of Medicine, University of Otago, New Zealand

The purpose of this paper is to present in a preliminary way some suggestions in regard to the pathogenesis of essential hypertension. An introductory historical review of the subject is omitted, as several reviews are available already.

1. Evidence that Physiological Elevation of Blood Pressure Predisposes to Essential Hypertension in Later Life

Even when the blood pressures lie within limits regarded as normal, individuals whose pressures are higher than the average have a higher-than-average incidence of hypertension and circulatory disorder in later life, whereas those whose pressures are below the average have a decidedly lower-than-average incidence of essential hypertension and of circulatory disorders in later life (Symonds, 1923; Association of Life Insurance Medical Directors and the Actuarial Society of America, 1925; Diehl and Hesdorffer, 1933; Trans. Internat. Congress Life Ass. Med., 1935; Actuarial Society of America, 1939; Robinson and Brucer, 1939; Hunter, 1939; Hines, 1940; Actuarial Society of America, 1941).

Reference will now be made to some of the factors influencing the blood-pressure level. Especial attention will be given to the relationship of such factors to the expectation of the development of essential hypertension in later life.

Race and Geographical Environment

European and North American white people have somewhat higher average and modal casual blood pressures than certain Indian, Chinese, African, Philippine, and American Indian peoples, and the incidence of high blood pressure is decidedly lower among the latter group. The differences between the average blood pressures of such groups may be 10 to 20 mm. systolic and 8 to 15 mm. diastolic for comparable ages. While race seems to influence the liability to essential hypertension (Kirk, 1931; Shattuck, 1933; Flaxman, 1934; Kean, 1941) environment also has a strong influence; and this predisposition seems to be closely related to the levels of the blood pressures encountered in the populations under consideration.

For example, China appears to provide an environment favouring lower blood pressures and less essential hypertension. North America favours higher levels of the "normal" blood pressures and much essential hypertension. The blood pressure of Chinese in China is below that of Canadian and United States citizens resident in their own countries (Cadbury, 1922, 1923; Ying, 1926; Kilborn, 1926; Foster, 1927; Tung, 1928, 1930). Essential hypertension in much of China is also uncommon (Cadbury, 1922, 1923; Cruickshank, 1923; Kilborn, 1926; Foster, 1927, 1930) even among well-fed sections of the community (Houston, 1929). Krakower (1933–4) states that the blood pressure of Chinese after long residence in Canada resembles that of other Canadian residents, and that essential hypertension is common. Tung (1928) found that 30 Chinese resident in the United States had falls of pressure on returning to Peking. Tung (1927) reported that 58 Americans had a distinct fall of blood pressure on taking up residence in China, and Foster (1927) found that 120 Americans in Hunan had an average pressure close to that of the local Chinese.

African negroes have lower blood pressures than those of their race who live in America (Donnison, 1929), and the incidence of high blood pressure is low among negroes in Africa (Heimann, Strachan, and Heyman, 1929; Shattuck, 1930; Schulze and Schwab, 1936). The latter authors also quote personal communications from Taylor, Odaley, Dry, and Wakeford. American negroes after the age of 20 have higher blood pressures than American whites (Alvarez and Stanley, 1930; Adams, 1932), and the incidence of high blood pressure is greater in negroes than in white residents of the United States (Stone and Vanzant, 1927; Donnison, 1929; Alvarez and Stanley, 1930; Allen, 1931; Holmes, 1931; Kirk, 1931; Adams, 1932; Laws, 1932–3; Flaxman, 1934; Weiss and Prusmack, 1938; Hedley, 1941). Hypertension of a few days' duration after exposure to explosive blast was more common in negroes than whites (Ruskin, Beard, and Schaffer, 1948). Hypertension is greater among town dwellers than among country dwellers of the same race and land (Holmes, 1931; Flaxman, 1934). East Africans also have lower blood pressures and less essential hypertension than North American or Western Europeans (Donnison, 1929; Williams, 1944a, 1944b). Egyptians on the whole have lower blood pressures than Anglo-Saxon peoples and a somewhat lower incidence of essential hypertension (Ismail, 1928; Smirk, unpublished observations). British residents in Egypt have slightly lower blood pressures than the average in Great Britain (Smirk, unpublished observations).

The blood pressure in Filipinos and in Porto Ricans is lower than in people of the United States (Concepción and Bulatao, 1916; Ashford and Dowling, 1929; Torgerson, 1929; Salcedo and Pascual, 1932; Lantin, 1933), and hypertension is probably less frequent (Ashford and Dowling, 1929; Torgerson, 1929; Lantin, 1933).

Among the poorer classes in India blood pressures are lower (McCay, 1907) and essential hypertension is less common than in Anglo-Saxon lands (Raghavan, 1941).

The South American Indians of Yucatan have low blood pressures and a low incidence of essential hypertension (Shattuck, 1933). The Cuna Indians, living relatively isolated, had an average pressure of 105/69 for 407 adults, and no case of hypertension was discovered among them (Kean, 1944). The Zuni Indians have low blood pressures and little hypertension (Fleming, 1924).

Hicks (personal communication) found a systolic blood pressure of 110 was the most common in young Australian aboriginals, and in 120 aboriginals between 60 and 65 he found no blood pressures higher than 130 systolic. Benign hypertension is not uncommon in Australian Whites. Nye (1937) also remarks on the low incidence of hypertension in Australian aboriginals.

Certain environments favour higher "normal" blood pressures and other environments favour lower "normal" blood pressures. Populations exhibiting higher "normal" blood pressures have a higher incidence of essential hypertension and those with lower "normal" blood pressures have a lower incidence.

Heredity

Heredity influences the level of the blood pressure. According to Ayman (1936), the children of two hypertensive parents have higher blood pressures and a 47% chance of essential hypertension in later life. When both parents are normotensive the blood pressures of the children are lower and the chance of essential hypertension is only 3%. This evidence is well supported by observations on identical twins, though environmental differences may sometimes lead to different blood pressures in identical twins. Additional evidence is cited by Platt (1947).

*The subject matter of lectures delivered as visiting Professor of Medicine at the British Postgraduate Medical School, Hammersmith.

Obesity

Obesity is statistically associated with over-average blood-pressure levels (Dublin, Fisk, and Kopf, 1925; Huber, 1927; Hartman and Ghrist, 1929; Kirk, 1931; Nuzum and Elliot, 1931; Short and Johnson, 1939; Robinson, Brucer, and Mass, 1940; Adlersberg, Coler, and Laval, 1946). This relation is found not only in the common forms of obesity but also in the obesity of Cushing's syndrome and in cortical hyperadrenia. Under-average body weight is associated with under-average levels of the blood pressure (Symonds, 1923; Huber, 1927; Robinson, Brucer, and Mass, 1940). Over-average blood pressures in children of over-average weight is also reported (Stocks and Karn, 1924; Short and Johnson, 1939). Manifest essential hypertension is also more frequent in the obese (Symonds, 1923; Terry, 1923; Dublin, Fisk, and Kopf, 1925; Barach, 1928; Master and Oppenheimer, 1929; Gager, 1930; Kirk, 1931; Nuzum and Elliot, 1931; Palmer, 1931; Short and Johnson, 1939; Robinson, Brucer, and Mass, 1940; Rony, 1940; Moschcowitz, 1945; Adlersberg, Coler, and Laval, 1946). Essential hypertension and obesity are to some extent genetically determined (Gates, 1946), although the relationship between them is scarcely understood (O'Hare, Walker, and Vickers, 1924; Page and Corcoran, 1945). Like twins exhibit very similar body weights (Rony, 1940), and their blood pressure is usually about the same level (Weitz, 1923; Hines, 1937–8; Klemola, 1938).

The relationship of obesity to hypertension, however, is not purely genetic, for loss and gain of weight from altered food intake are associated with fall and rise of blood pressure. This relationship between alteration in body weight and blood pressure has been observed in the obese and in persons of normal weight, in normotensives (Benedict, 1915; Benedict, Miles, Roth, and Smith, 1919; Preble, 1923; Bauman, 1928; Master and Oppenheimer, 1929; Moschcowitz, 1945), and in hypertensives (Preble, 1923; Rose, 1923; Terry, 1923; Master and Oppenheimer, 1929; Moller, 1931; Moschcowitz, 1945; Adlersberg, Coler, and Laval, 1946). In normal dogs and in hypertensive (Goldblatt, 1947) dogs, Wood and Cash (1939) showed that gains and losses of weight were associated with rises and falls of blood pressure. The effect of overweight on the blood pressure in man seems to be more pronounced after 40, corresponding to the age when the incidence of essential hypertension rises.

The blood-pressure fall corresponding to an average reduction of 24 lb. (10.4 kg.) was about 32 mm. systolic and 16 mm. diastolic in the 72% of obese hypertensives in the series of Adlersberg, Coler, and Laval (1946), who had a fall of blood pressure. The difference in the average blood pressure between more or less unselected groups of overweight and underweight individuals is about 10 mm. systolic and 8 mm. diastolic. The effect of obesity is more obvious, however, when the comparison is made between the percentage of hypertensives encountered in individuals who are over the normal standard weight as compared with the percentage among subjects who are under the normal standard weight.

It is clear that overweight is associated with a tendency to higher blood-pressure levels, and in the course of time a higher incidence of essential hypertension. Under-average weight is associated with lower blood pressures and decreased tendency to essential hypertension in later life. Errors in blood-pressure measurement by cuff methods and due to upper-arm obesity require further evaluation.

Transient Blood Pressure Increases

Of the blood pressure rises which occur in response to emotion most are transient, but many are of longer duration (von Monakow, 1920; Fahrenkamp, 1926; Weitz and Sieben, 1926; Grollman, 1929; Houston, 1929; Brown, 1929–30; Alkan, 1930; Mueller and Brown, 1930; Stieglitz, 1930; Kronfeld, 1932; Schultz, 1932; Ayman and Goldshine, 1940; Alam and Smirk, 1943a, 1943b; Ehrström, 1945). Emotional rises of pressure of 10 or 20 mm. are common, and rises of 50 mm. or more are encountered.

Such transient pressure increases are exhibited particularly on the first visit in connexion with an examination for military service, life assurance, student health survey, or clinical examination. That most of these transient rises are due to emotion, tenseness, alertness, or some such mental state is very highly probable, because nearly all subside, sometimes in a few minutes, if the subject can be put at ease (Weitz and Sieben, 1926; Mueller and Brown, 1930; Ayman and Pratt, 1931; Alam and Smirk, 1943a, 1943b; Smirk, 1944, 1947; Kilpatrick, 1948). The pressure often can be made to rise promptly again if emotion be provoked, for example, by a tactless remark or the entry of a nurse with a tray of instruments (Alam and Smirk, 1943a; Kilpatrick, 1948). Those who exhibit such transient blood-pressure elevations have a much greater chance of developing permanent arterial hypertension later (von Monakow, 1920; Frost, 1926; Palmer, 1930; Stieglitz, 1930; Robinson and Brucer, 1939; Hines, 1940). Even in young people transient rises carry an enhanced expectation of developing essential hypertension later (Palmer, 1930; Diehl and Hesdorffer, 1933; MacKenzie and Shepherd, 1937; Master, 1943; Rogers and Palmer, 1944; Levy, White, Stroud, and Hillman, 1945a, 1945b).

I am aware of no evidence which points to the existence of any pathological process in young subjects exhibiting transient hypertension and which might explain it. Transient blood-pressure elevations in otherwise healthy individuals under the age of 25 probably represent physiological responses of a magnitude greater than average. These might occur if vasomotor reactions or the mental reactions to physical stimuli or stress are excessive.

The reactions to vasomotor reflexes, such as the cold pressor test of Hines and Brown (1935), and the blood-pressure-raising reflex from voluntary muscle (Alam and Smirk, 1937) are usually greater in cases of essential hypertension than in healthy subjects of the same age group (Alam and Smirk, 1938). The elevations of blood pressure in response to psychical stimuli and in response to cold do not invariably show parallelism (Ruskin, Beard, and Schaffer, 1948). Hines and Brown (1935) state that the pressure-rises in response to cold are greater in the children of hypertensive parents than in those of normotensive parents. They consider that hyper-reacting normotensives are more likely to develop hypertension in later life. Evidence in the same direction comes from Dieckmann and Michel (1935). Evidence against the views of Hines and Brown has been published (Pickering and Kissin, 1936; Yates and Wood, 1936; Feldt and Wenstrand, 1942; Russek, 1943; Russek and Zohman, 1945). The matter is not yet settled.

Not all patients respond to nervousness or tenseness by blood-pressure rises (Hall, 1927), but those who do, and whose environment causes nervous tension, may be expected to exhibit those increases more often than normal individuals. Fischer (1930) states that mental exertion unaccompanied by emotion had no notable effect on the blood pressure, whereas Hill (1898), Bickel (1914), and Gillespie (1924) report that mental work elevates the blood pressure. Changes in the mental state of melancholic and other psychotic and psychoneurotic patients may be associated with considerable alterations in the blood pressure (Mueller, 1922). There are large individual differences in the reactions to mental stimuli, but many authors consider essential hypertensives are over-reactive, overtense physiological types (Moschcowitz, 1919; Ayman, 1933; Menninger, 1938; Binger, 1945).

No doubt transient hypertension is due in many cases to a combination of vascular lability with emotional lability, but sometimes one or other of these will predominate. The more restless and competitive environment of urban as distinct from rural life has been held responsible in American negroes and whites for the higher incidence of essential hypertension in urban communities (Holmes, 1931; Hashimoto, Akatsuka, Tsujii, and Shiraishi, 1933–4; Schulze and Schwab, 1936). Stocks and Karn (1924) state that the average blood pressure of children is higher in schools with strict discipline than in those where discipline is lax. Tigerstedt (1926) refers to the higher blood pressures in students in the few weeks before an examination. Ruskin, Beard, and Schaffer (1948) report considerable hypertension of some days' duration in persons exposed to explosive blast. Fraser and Cowell (1918) refer to the higher level of the blood pressure in front-line troops

when compared with supporting troops, and somewhat similar results have been reported by others (Gelshtein, 1943; Ehrström, 1945; and Graham, 1945). It has been claimed by Farris, Yeakel, and Medoff (1945) that repeated exposure of rats to an air blast may set up a lasting arterial hypertension. This has been confirmed by Restall and Smirk (unpublished observations), who have shown also that this hypertension is not abolished by anaesthesia.

The tendency to exhibit transient hypertension in response to mental and other stimuli may be taken to indicate a physiological make-up which is likely to express itself in daily life by abnormally strong and frequent blood-pressure elevations. The balance of evidence suggests that such elevations, if sufficiently frequent or prolonged, predispose the subjects towards the development later of essential hypertension.

2. Casual, Basal, and Supplemental Pressures

If the level of the blood pressure in health is an important indication of the future liability to essential hypertension, it will be important to know what significance should be attached to single or to multiple readings of the blood pressure.

The blood-pressure level in a ward or consulting-room is not an accurate guide to the average blood pressure of the patient throughout the day and during the night (Brooks and Carroll, 1912; Müller, 1921; MacWilliam, 1923; Campbell and Blankenhorn, 1925–6; Friedlander, 1927; Ayman, 1931; Master, 1943; Gubner, Silverstone, and Ungerleider, 1946). Were it possible to obtain some indication of the average of the pressures to which the vascular system was exposed a much closer correlation between this average pressure and the subsequent development of essential hypertension might be possible. It is, however, possible to discover the ranges over which the blood pressure is likely to fluctuate.

The blood pressure, even in health, is not to be regarded as an indivisible unity but as having two components. If the blood pressure (systolic and diastolic) taken under ordinary clinical conditions be considered as the casual blood pressure and that taken under defined basal conditions as the basal blood pressure, the difference between the casual and the basal blood pressure may be described as the supplemental pressure (Alam and Smirk, 1943a; Smirk, 1944). The supplemental blood pressure is, by definition, that part of the casual blood pressure which represents the response to the person's physical, metabolic, and cerebral activity at the time of measuring the pressure. Kilpatrick (1948) has confirmed and extended my observations on the basal blood pressure and has shown that in health the basal blood pressure is a physiological constant for the individual. In a series of 50 normal subjects (Smirk, 1944) the basal and supplemental pressures were independent variables in the sense that the possession by an individual of a high basal pressure neither increased nor appreciably diminished the expectation of that individual having a high supplemental pressure. Analysis of further experiments by Kilpatrick gives the same result. In a sense, therefore, among normals a person comes into the higher pressure range through the statistical coincidence of having both a high basal and a high supplemental pressure.

During undisturbed dreamless sleep the supplemental pressure falls to, or almost to, zero, whereas the basal pressure is substantially unaffected. The cardiovascular strain will be less if a given level of the casual blood pressure is derived from a low basal pressure and high supplemental pressure than if the reverse holds. Clinical experience (Alstad and Smirk, unpublished) suggests that high casual blood pressures due chiefly to a higher basal pressure are of more serious significance than casual blood pressures of equal height caused chiefly by an increase in the supplemental pressure, but the latter may be associated with pathological sequelae of hypertension.

Further relevant observations on basal and supplemental pressures have been reported elsewhere (Alam and Smirk, 1943a, 1943b; Smirk, 1944, 1947; Kilpatrick, 1948). Statements are made that blood pressures over 135 in young adults are to be regarded as abnormal. It is suggested that the decision rests to some extent on our concept of abnormal. I believe some confusion would be avoided if the decision about the normality or abnormality of a blood-pressure level were held to depend upon whether it is attained through the normal operation of physiological processes or whether it is elevated to some extent by pathological processes. Moderate elevations of the blood pressure may at first be induced entirely by the operation of physiological processes. Some of these physiological processes are intrinsic and represent a physiological set or a resultant of the many intrinsic factors influencing blood pressure. Some factors influencing the blood pressure, such as geographical and social environment, are extrinsic, and others, such as obesity, are probably both intrinsic and extrinsic.

The hypothesis suggested by the circumstantial evidence outlined above is that physiological elevations of the blood pressure, if high enough or of sufficient duration, predispose strongly to, or in some cases cause, the development of a pathological elevation of the blood pressure—namely, essential hypertension. Those influences which lead to elevation of the basal pressure probably predispose more strongly to the subsequent development of essential hypertension than influences which elevate only the supplemental pressure.

3. Evidence that in Essential Hypertension Blood-pressure Elevation Sometimes Precedes the Development of Arteriolosclerosis

The evidence comes partly from the many clinical reports of high-blood-pressure tendencies at an early age, when primary pathological changes in the vessels are unlikely (Glomset, 1931; Ayman, 1934; Hines, 1940; Kerley and Lorenze, 1942; Levy, Hillman, Stroud, and White, 1944; Graham, Hines, and Gage, 1945; Platt, 1948), and partly from histological and renal function studies. The temporary nature of the blood-pressure rises initially also suggests that an established humoral mechanism (e.g., Goldblatt) is not operating at this early stage.

Cases of essential hypertension in which the kidney taken at necropsy was normal have been reported by many authors (Pal, 1919; Bell and Clawson, 1928; Moritz and Oldt, 1937; Fishberg, 1939; Garreton-Silva, Rodríguez, and Aspillaga, 1941), although most of them regarded this as an exceptional finding. When, however, cases are selected deliberately from patients in the early stages of the disorder, normal kidneys or those showing minimal changes are often encountered (von Monakow, 1920; Wallgren, 1922). Thus kidney samples from early cases, removed at biopsy in the course of sympathectomy operations by Castleman and Smithwick (1943), have shown few of the findings characteristic of the more advanced cases encountered at necropsy.

Scott (1944) and Goldblatt (1947) criticized Smithwick (1944), in that his biopsy samples were too small. Smithwick's histological observations, however, are supported by the finding of almost normal diodrast excretion, which corresponds with results published by Page and Corcoran (1945). My histological observations on post-mortem material from moderate hypertensives under the age of 40, and dying of unrelated disorders, suggest that recognizable defects in arterioles may be lacking. Where

arteriolar changes were found they were much less in degree than those exhibited by the arterioles of elderly normotensives.

Cox and Dock (1941) perfused the kidneys of patients with essential hypertension and of controls and found the flow through the kidneys decreased with age, the decrease being but little greater with essential hypertension kidneys than with control kidneys from the same age group. Kimmelstiel (1933), perfusing kidneys, found little vascular obstruction in many early cases of benign hypertension, with equal or greater vascular obstruction in some elderly normotensives. McGeorge (1945) demonstrated a decrement in the renal function with increasing age, and pointed out that the renal function of young hypertensives was similar to that of young normotensives and both exhibited a better capacity to concentrate urea and chloride simultaneously (Smirk, 1933–4, 1934) than either old normotensives or old hypertensives. The decrease in renal function progresses more rapidly in cases of essential hypertension than in non-hypertensive controls. It seems very probable that the decrements in renal function with advancing years in normotensives and in essential hypertensives are due largely to decrease with age in the blood supply to the kidneys, with a more rapid decrease in the latter. Aitken in his unpublished work for a New Zealand M.D. thesis in 1944 undertook at my suggestion some observations on injected specimens of kidneys from young subjects of essential hypertension and also found the vascular beds to be substantially normal.

Indeed, it would seem that the evidence of gross pathology, microscopical pathology, intra-arterial injection studies of kidneys, biopsy studies of kidneys, perfusion of dead kidneys, renal function tests of various kinds, and the intermittent character of the blood-pressure increase in its early stages all suggest that the degree of permanent renal ischaemia in the early stages of essential hypertension *in young subjects* is unimportant and is not to be regarded as an adequate explanation of the blood pressure increases. *The evidence available at the present time suggests that when the disorder starts or when a "prehypertensive" state is present in comparatively young people the elevation of the blood pressure is often, probably usually, manifest before the characteristic pathological changes make their appearance in the kidney and in other organs.*

In many patients, however, the blood pressure does not start to rise appreciably until after the age of 40 or 50. When the blood pressure first rises after the age of 45 pathological changes in renal arterioles of one kind or another will almost certainly be present before the blood-pressure increase has reached the level ordinarily regarded as abnormal. It is possible, therefore, that in at least some of the cases in which the blood pressure begins to rise appreciably for the first time in middle life the renal ischaemia may have initiated the increase.

4. Evidence that High Blood Pressure Accelerates or Causes the Development of Arteriolosclerosis

In almost every muscular organ an increase in work beyond the physiological range of any kind of muscle—cardiac, voluntary, or involuntary—leads to hypertrophy. The cardiac hypertrophy in hypertension and the development of voluntary muscles with physical labour are well known. In the alimentary, urinary, and biliary tracts partial obstruction leads to hypertrophy of the muscle behind the obstruction. In the larger vessels of well-established cases of essential hypertension hypertrophy of the media is encountered. Vascular hypertrophy is seen in small pulmonary arteries obstructed by the bilharzia ova (Shaw and Ghareeb, 1938).

The walls of veins hypertrophy when exposed to raised pressure in arteriovenous aneurysm, the portal veins in cirrhosis of the liver, and the great systemic veins in congestive heart failure (Pei-Lin Li, 1940). In high blood pressure of varying types, essential hypertension, glomerulonephritis, pyelonephritis, polycystic kidneys, medullary hyperadrenia, cortical hyperadrenia, and in experimental hypertension of different types the typical thickening in the walls of arterioles has been described. Such changes may occur even in young children with hypertension of various origins. It seems that this hypertrophy also is due to the effect of increased pressure on the walls of blood vessels. Although the vast majority of observations strongly favour the idea that high blood pressure can cause hypertrophy of the walls of arterioles and of larger arteries a certain amount of evidence is either opposed to or fails to support this idea. In coarctation of the aorta it is stated (Graybiel, Allen, and White, 1935) that the arterioles in muscle samples taken in the upper part of the body showed no hypertrophy when compared with muscles taken from the lower part of the body. On the other hand, arteriolar hypertrophy in coarctation cases has been reported (Heyer and Keeton, 1941).

Again, there are a number of instances in the literature of high blood pressure of appreciable duration with few changes in the arterioles. In experimental hypertension in animals of various types arteriolar changes are sometimes found and sometimes lacking (Hamperl and Heller, 1934; Wilson and Pickering, 1937–8; Wilson and Byrom, 1939). Negative results may mean that there has not been enough time for hyperplasia or that the degree of increase in the blood pressure was insufficient. It seems that the dog often can tolerate prolonged experimental hypertension without exhibiting substantial arteriolar changes; on the other hand, it has been shown by Wilson and Byrom (1939), in the rat, that high blood pressure induced by ischaemia of one renal artery may lead to typical changes in the arterioles of the non-ischaemic kidney.

The observations of Wilson and Byrom were not accepted by Goldblatt and Kahn (1940), on the grounds that white rats are particularly susceptible to pyelonephritis, and the latter workers considered that the results obtained might have been explained by the development of this condition. Restall (unpublished observations) has shown that rats rendered hypertensive for a period of approximately one year by unilateral renal ischaemia exhibit arterial changes in the other kidney. His histological observations and the bacteriological studies by Kirschner rule out pyelonephritis in most of the experiments.

That high blood pressure gives rise to medial hypertrophy in the smaller arteries and in arterioles may be regarded as proved. There is also evidence that other arteriosclerotic changes, such as increase of elastic tissue and perhaps intimal hyperplasia (Restall, unpublished observations), may develop as the result of increased intravascular tension. The literature is summarized by Hueper (1944). The arteriolar changes secondary to high blood pressure are usually more pronounced in the kidneys than in other organs.

5. Ways in which Pathological Changes Induced or Accelerated by Hypertension may lead to Further Elevation of Blood Pressure

It seems probable that, irrespective of the cause, prolonged elevations of the blood pressure of sufficient degree, both physiological and pathological, tend to be followed by processes which lead to the further elevation of the blood pressure, with the ultimate development of essential hypertension. Any pathological or physiological changes brought

about by the primary hypertension and leading to secondary rises of blood pressure could set up a vicious circle. At least five such mechanisms must be discussed.

(i) Inelasticity of Larger Arteries

In hypertension, arteriosclerosis of great vessels is accelerated with the loss of distensibility (Bramwell, 1924; Fahr, Davis, Kerkhof, Hallock, and Giere, 1932; Wiggers, 1938) causing systolic hypertension. It is stated that the mean blood pressure is not raised (Fahr, Davis, Kerkhof, Hallock, and Giere, 1932), and therefore it is uncertain whether such hypertension will or will not tend to accelerate arteriosclerosis and arteriolosclerosis further. *It is not suggested that this systolic hypertension caused by decreased elasticity of large arteries is sufficient to explain the progressive increase of blood pressure, but that it is a factor which participates.*

(ii) Exaggerated Contraction of Hypertrophied Arterioles

Measurements of arterioles and small arteries in almost all tissues of the body, and notably in muscle, indicate that at a certain stage in the development of essential hypertension there is medial hypertrophy. It seems likely that more vigorous responses by hypertrophied blood vessels would account for the fact that both rises and falls of blood pressure in response to various stimuli are commonly exaggerated in essential hypertension. Experimental evidence in favour of this has been obtained by Restall (unpublished observations), who compared the response to adrenaline of blood vessels from chronically hypertensive and control rats, and found greater responses from the vessels of hypertensives, especially renal vessels. Even if medial hypertrophy does not of itself raise the blood pressure it seems probable that it would render other hypertensive agents more effective. *If the medial hypertrophy caused by blood-pressure elevations leads to further increase of the blood pressure another vicious circle has been set up.*

(iii) The Goldblatt Mechanism and Variable Reactivity of Blood Vessels to Pressor Agents

The suggestion has been made that essential hypertension might be due to the liberation of pressor substances from kidneys rendered ischaemic by arteriolar changes in the renal blood vessels (Goldblatt, 1947). The arteriolar changes in essential hypertension are most prominent in the kidney (Fahr, 1922; Fishberg, 1925; Russell, 1929; Moritz and Oldt, 1937; and others). I favour the view that such arteriolar changes, more particularly in the later years, may occur primarily, but some at least of them may be caused or accelerated by the prodromal rises of blood pressure referred to in the first part of this paper.

The experimental evidence that ischaemic kidneys sometimes liberate pressor substances is so strong that it may be taken as proved. The presence of some degree of renal ischaemia in almost all advanced cases, especially elderly cases, may be regarded as established. It seems probable that such renal ischaemia will cause a rise in blood pressure at certain stages and in certain cases of established essential hypertension. The suggestion has been made also that functional renal vasoconstriction might initiate a Goldblatt type of hypertension (Goldring, Chasis, Ranges, and Smith, 1941). At my suggestion Restall (unpublished observations) studied the response to adrenaline of blood vessels in rats rendered chronically hypertensive by unilateral renal ischaemia and in control rats. He found that vasoconstriction was much more pronounced in the vessels of the unoperated kidneys of the hypertensives than in the renal vessels of controls. Such observations indicate a means by which renal vascular changes may become progressive.

On the other hand, renal ischaemia is not always associated with an elevation of the blood pressure (Kimmelstiel, 1933; Cox and Dock, 1941). Whether the absence of hypertension is due to failure of the kidneys to release pressor agents, to the subsequent inactivation of such agents (Fasciolo, Houssay, and Taquini, 1938; Katz, Mendlowitz, and Friedman, 1938; Rodbard and Katz, 1941), to the operation of homoeostatic controls preventing an elevation of the blood pressure, or even to antipressor agents, it is impossible to say at the present time. The experimental study of renal hypertension is made more difficult by the fact that the available experimental animals behave dissimilarly (Braun-Menéndez, Fasciolo, Leloir, Munoz, and Taquini, 1946). In the rat and rabbit it has been suggested that, whereas the initial rises of blood pressure following renal ischaemia are due to the Goldblatt mechanism, the subsequent maintenance of the high blood pressure is effected by some other means. The application of the results to human hypertension remains uncertain. The processes whereby renal ischaemia leads to hypertension in experimental animals is complicated and not yet fully evaluated. Liberation of an enzyme-like substance, renin, from the ischaemic kidney acts upon a substrate-like substance, preangiotonin, which is a constituent of plasma, to form a pressor agent, angiotonin. The angiotonin causes vasoconstriction by a direct action on smooth muscle, but has a limited period of action owing to its enzymic destruction.

From the observations of Black (unpublished) it seems that, apart from destruction, the amount of circulating angiotonin could not be the only factor deciding the magnitude of blood-pressure increase. Black has shown that there is no consistent difference between hypertensives and normotensives in respect of their sensitivity to the pressor action of intravenous angiotonin. Some individuals are insensitive to doses of angiotonin which in others cause large rises in blood pressure. Vascular sensitivity to the pressor action of angiotonin runs parallel with sensitivity to the pressor action of S. methyl isothiourea. A non-specific reactivity of blood vessels governs the pressor response as well as the amount of circulating angiotonin.

The formation of hypertensive agents depends upon the degree of ischaemia and the amount of renal tissue involved; and the rate of destruction of hypertensive agents is related to the amount of non-ischaemic renal tissue in the body. The kidneys both of essential hypertension and of elderly normotensive cases may have within them areas which are ischaemic and areas which are adequately supplied with blood. It is therefore possible that while parts of the renal tissue are forming, other parts may be destroying, the hypertensive agents. Increased formation of V.E.M. or decreased elimination of pressor amines by amine oxidase have been suggested as alternative or additional mechanisms by which renal ischaemia could cause blood-pressure elevations. *It seems clear, however, that elevated blood pressure favours renal arteriolosclerosis, and if this in turn gives rise sometimes to further elevations of the blood pressure due to the renal ischaemia a vicious circle would be set up.*

(iv) Elevations of the Blood Pressure Persisting After the Initial Cause has Ceased to Operate

(*a*) *Hypertension Persisting After Removal of a Single Ischaemic Kidney.*—In the rat the removal of the ischaemic kidney after several months of experimental hypertension did not usually restore the blood pressure to normal (Wilson and Byrom, 1941; Grollman, Harrison, and Williams, 1943; Patton, Page, and Ogden, 1943). It seems that in many cases pathological changes have developed in the unoperated kidney (Patton, Page, and Ogden, 1943; Restall, unpublished observations), and the persistence of the blood-pressure elevation has been attributed to these. Pickering (1945) has indicated the possibility of a non-renal mechanism. Likewise in the rabbit Grollman (1944) found that nephrectomy after ten weeks of hypertension from renal compression does not abolish the hypertension. In the dog the evidence is insufficient. It has been shown that removal of a single ischaemic kidney abolishes the hypertension in the dog if the removal is carried out within the first few weeks (Goldblatt, Lynch, Hanzal, and Summerville, 1934; Blalock and Levy, 1937; Houssay and Fasciolo, 1937; Verney and Vogt, 1938, 1943; Rodbard and Katz, 1939). Isolated experiments suggest that, in the dog, hypertension may persist if removal of the ischaemic kidney is postponed for three months or more. Goldblatt, however, reported an experiment in a dog with unilateral renal hypertension of nine months' duration which was completely cured by nephrectomy.

(*b*) *Hypertension Persisting After Bilateral Nephrectomy.*—Pickering (1945) has shown that blood-pressure elevations may be made to outlive the stimulus which produced them. He raised the blood pressure in rabbits by unilateral nephrectomy and constriction of the main artery of the remaining kidney, and noted that if hypertension had lasted but a few days and

the remaining ischaemic kidney was removed the blood pressure fell to normal in a few hours. If the hypertension had lasted seven weeks or more excision of the ischaemic kidney no longer removed the hypertension. The response of the blood vessels was altered as the result of the prolonged hypertension. There are clinical experiences which may be analogous. For example, where the blood-pressure rise due to toxaemia of pregnancy has been of short duration, even if high, termination of the pregnancy often is associated with a comparatively rapid fall of the blood pressure back towards normal. If, however, the blood-pressure rise has been of long duration the blood pressure may not return to normal for several months after the termination of the pregnancy, and in some cases a permanent hypertension results. The incomplete fall or absence of a fall of blood pressure following the removal of a unilateral ischaemic kidney even when there is good evidence that the remaining kidney is healthy (Abeshouse, 1941a, 1941b) may be another example.

Some observations concerning the effect of bilateral nephrectomy by Flemming (unpublished observations) on hypertensive rabbits confirm the observations of Pickering.

(*c*) *Experimental Audiogenic and Neurogenic Hypertension.*—Medoff and Bongiovanni (1945) and Farris, Yeakel, and Medoff (1945) showed that rats subjected for long periods to intense intermittent audiogenic stimuli developed elevations of blood pressure. Restall and Smirk (unpublished observations) confirmed these findings and found in agreement with Medoff and Bongiovanni that the blood-pressure elevations were not abolished by light or ether anaesthesia. We noted that the blood-pressure increase persisted for at least several months after the audiogenic stimulation ended, that there was no histological evidence of renal damage in the early stages of the experimental hypertension, and that the blood pressure remained elevated for 36 hours after bilateral nephrectomy. The possibility that the nervous system was damaged by supersonic waves has not yet been eliminated.

In some other experiments, however, rats were exposed first to a signal noise (buzzer), no question of supersonics being involved. The signal noise was followed by electrification of the cage causing a mild-to-moderate faradic stimulation of the rats' feet. This also led within a few weeks to a rise of blood pressure, though of smaller degree, which was not abolished by light ether anaesthesia. It seems that the initial blood-pressure elevation is due in this case to nervous stimulation, and that this has given rise to an increase in blood pressure which apparently is maintained by some process other than that which initiated the hypertension.

This would appear to be experimental confirmation in the rat of the suggestion that certain blood-pressure increases if frequent or prolonged enough may outlive the stimuli which caused them. These persisting blood-pressure increases in rats following audiogenic and electrical stimulation often persist after bilateral nephrectomy, and in this resemble those described by Pickering (1945) in rabbits after hypertension induced by renal ischaemia. Apart from the general resemblance there is as yet no evidence of a single underlying mechanism. The significance for human hypertension is undetermined.

(v) Absence of Appreciable Increase of Passive Resistance in Hypertrophied Vessels

The idea that pathological changes in the arterioles may result in a permanent increase in the peripheral resistance and thereby be responsible for continued elevation of the blood pressure was discussed by Volhard (1931). The elevation was looked on as being passive and anatomical rather than contractile in origin. The changes in the blood vessels outside the kidney, however, are thought to be insufficiently advanced to give support to this explanation. The considerable fall in blood pressure which may occur for a short time after sympathectomy, after nitrates, or from thiocyanate overdosage suggests that no great part of the peripheral resistance is the result of purely passive changes in the vascular bed. Restall perfused through the aorta the hind quarters of rats which had been hypertensive for a period of 12 to 18 months (approximately one-third to one-half of the normal duration of a rat's life), and, compared with normal rats, he found but little difference in the peripheral resistance. It appears from this experiment that the continued high blood pressure was maintained by active vasoconstriction and even after one year only a minor part of the peripheral resistance of the lower limbs was of a passive character. *I have not, therefore, been able to find experimental support for the idea that pathological changes in vessels lead in time to the development of any important generalized increase of passive peripheral resistance.*

6. Other Factors which may Elevate the Blood Pressure

1. *Increased Reactivity to Blood-Pressure-Raising Reflexes in Cases of Arterial Hypertension.*—High reactivity to the cold pressor test (Hines and Brown, 1935) and to the blood-pressure-raising reflex from muscle (Alam and Smirk, 1938) is often encountered in essential hypertension, but this does not by itself explain a high level of the *resting* blood pressure. It is probable that a high degree of reactivity of the blood pressure to blood-pressure reflexes may express itself in daily life by abnormally strong and frequent blood-pressure variations. The blood pressure from this cause may be found at a higher level in the non-basal conditions which ordinarily are present at the time of measurement. The reactivity to blood-pressure-raising reflexes increases with age, but to a greater degree in essential hypertension than in health (Alam and Smirk, 1938 ; Russek and Zohman, 1945).

2. *Natural Increase of Blood Pressure with Age.*—The recorded blood-pressure averages increase with age. To some extent this is due to the effect of including the pressures of hypertensive individuals in the figures. The general impression, however, is that there is also an increase in the average blood pressure with age which does not depend on the inclusion of hypertensives. This "natural" blood-pressure increase with age is likely to be one of the several factors responsible for the increase in the incidence of essential hypertension in the later years of life.

3. *Alteration in the Response of the Carotid Sinus to Blood-Pressure Increase.*—While my observations confirm Pickering, Kissin, and Rothschild (1936) in their view that the carotid sinus mechanism in cases of essential hypertension responds to digital stimulation, I found that in response to blood-pressure increases produced reflexly the pulse rate tends to rise instead of falling in most cases of essential hypertension, the natural relationship between pulse rate and blood pressure being reversed (Alam and Smirk, 1938). A corresponding observation was made previously by MacWilliam (1925). A possible interpretation of this is that the carotid sinus offers a less effective control over the blood-pressure level in cases of essential hypertension.

4. *Increase of the Secretions of the Suprarenal Gland.*—The suggestion has been made that cortical hyperadrenia may be concerned in the pathogenesis of essential hypertension (Perera, Knowlton, Lowell, and Loeb, 1944 ; Perera and Blood, 1947a, 1947b). In terms of the present hypothesis, blood-pressure increases of suprarenal origin or any other, if sufficiently frequent and prolonged, would be expected to play their part in pathogenesis.

Comment

If elevation of the blood pressure in essential hypertension depends upon the total effect produced by the combined action of several components, it becomes important to know whether the magnitude of the total effect is equal to the sum of the effects of the various components acting separately. The answer appears to be that the blood-pressure rise produced by two blood-pressure-raising stimuli acting simultaneously is less than the sum of the blood-pressure rises produced by the two stimuli acting separately (Bruce, Martin, and Smirk, 1945). This may be a part of the

explanation of why the rate of increase of the blood pressure is slowed up as higher levels are attained.

No reference has been made earlier in this paper to malignant hypertension, largely because it is thought that malignant hypertension is something other than a severe or accelerated form of essential or benign hypertension. After a survey of 169 consecutive deaths in hypertensive individuals, residents of the province of Otago, New Zealand, and on the basis of clinical experience in that province, Alstad and Smirk (1948) reached the conclusion that, whereas benign hypertension is a very common condition, malignant hypertension and the classical advanced glomerulonephritis are both most exceptional, particularly the former. It is sometimes stated that malignant hypertension is an accelerated form of benign hypertension. But experience goes to show that benign hypertension in Otago province does not differ fundamentally from benign hypertension in other countries, although its course appears to be rather milder; yet malignant hypertension is decidedly uncommon. It seems very probable, therefore, that the condition of malignant hypertension is not merely an accelerated form of benign hypertension but involves some additional factor over and above those responsible for benign hypertension. It is of great interest that there is also a correspondingly low incidence of chronic glomerulonephritis in Otago province. It is clearly worth considering whether the infrequency of advanced chronic glomerulonephritis and of malignant hypertension in this province is in some way related to the absence of a common aetiological factor.

Summary

It seems probable that there is no single or simple primary cause of essential hypertension.

It is thought that the disorder may originate in some cases from the simple overactivity of physiological processes, whereas in other cases pathological changes such as renal arteriolosclerosis may be primary.

It is suggested that the blood-pressure increases are of composite origin but that these increases, if frequent, high, or prolonged enough, give rise to a number of pathological and functional changes which tend to maintain or elevate the blood pressure further. Once this self-perpetuating cycle of changes has been set up the condition may be described as essential hypertension. Under-average blood pressures are associated with a much decreased incidence of essential hypertension in later life. It is difficult to explain this protective influence of low blood pressure except by the hypothesis that the tendency to develop high blood pressure in later life is influenced strongly by the precise level of the blood pressure even when this lies within the normal range.

Examples of factors various combinations of which may raise the level of the blood pressure enough to enhance strongly the liability to the subsequent development of essential hypertension include: certain geographical environments, race, heredity, emotional lability or disposition to over-alertness and tenseness, occupations or domestic environments involving a tendency to stress and strain, over-average liability of the vasomotor system to respond by vasoconstriction to tenseness and emotion, physical activity or metabolic stimuli, over-average body weight or sthenic habitus.

Elevations of the basal pressure are likely to throw greater strain on the heart and on small arteries and arterioles than are elevations of the supplemental pressure.

The degree to which blood vessels are able to withstand exposure to over-average blood pressure or vasoconstriction without undergoing pathological change varies from one individual to another and is likely to have an important influence both on the rate of increase of the blood pressure and on the development of complications.

Examples of a number of pathological and functional changes which in various combinations it is thought might be responsible for further elevations of the blood pressure are cited and discussed in the text. These include: (*a*) inelasticity of large arteries; (*b*) exaggerated contraction of hypertrophied arterioles; (*c*) the release of pressor agents from ischaemic kidneys; (*d*) to a very minor degree, increased passive resistance of hypertrophied arterioles; and (*e*) an unknown non-renal factor or factors capable of perpetuating certain blood-pressure increases after the primary exciting causes of these increases have ceased to operate. Other factors are referred to which probably contribute increments of pressure increase.

The fundamental unity of the clinical picture in essential hypertension is not dependent upon the blood-pressure elevation being regarded as the result of a single or simple pathological process. It is due to the fact that the clinical manifestations and complications are due almost entirely to events which are secondary to a single characteristic of the disorder —namely, high blood pressure brought about mainly by vasoconstriction.

The above general hypothesis holds that elevations of blood pressure in man and certain other mammals tend to be self-perpetuating. It is to be expected, therefore, that the cycles of changes concerned in the secondary elevations of the blood pressure which occur in essential hypertension will be responsible *in part* for the perpetuation, and perhaps for the further increase, of blood pressure in certain other conditions such as post-toxaemia of pregnancy, cortical hyperadrenia, and some cases of chronic pyelonephritis, medullary hyperadrenia, and chronic nephritis.

There is evidence suggesting that malignant hypertension is something other than an accelerated form of benign or essential hypertension.

Grateful acknowledgment is made to Miss Walsh and Mrs. Tyson for extensive secretarial help, and to the Medical Research Council of New Zealand for grants-in-aid.

References

Abeshouse, B. S. (1941a). *Surgery*, **9**, 942.
—— (1941b) Ibid., **10**, 147.
Actuarial Society of America and the Association of Life Insurance Medical Directors (1939). Blood Pressure Study.
—— (1941). Supplement to Blood Pressure Study.
Adams, J. M. (1932). *Amer. J. med. Sci.*, **184**, 342.
Adlersberg, D., Coler, H. R., and Laval, J. (1946). *J. Mt Sinai Hosp., N.Y.*, **12**, 984.
Alam, M., and Smirk, F. H. (1937). *J. Physiol.*, **89**, 372.
—— —— (1938). *Clin. Sci.*, **3**, 259.
—— —— (1943a). *Brit. Heart J.*, **5**, 152.
—— —— (1943b). Ibid., **5**, 156.
Alkan, Leopold (1930). *Anatomische Organkrankheiten aus seelischer Ursache*. Hippokratesverlag, Stuttgart. Cited by Dunbar (1935).
Allen, F. P. (1931). *J. industr. Hyg.*, **13**, 164.
Alstad, K. S., and Smirk, F. H. (1948). *N.Z. med. J.*, **47**, 298.
Alvarez, W. C., and Stanley, L. L. (1930). *Arch. intern. Med.*, **46**, 17.
Ashford, B. K., and Dowling, G. B. (1929). *P.R. J. publ. Hlth*, **5**, 477.
Association of Life Insurance Medical Directors and the Actuarial Society of America (1925). Blood Pressure, Report of the Joint Committee on Mortality.
Ayman, D. (1931). *New Engl. J. Med.*, **205**, 424.
—— (1933). *Amer. J. med. Sci.*, **186**, 213.
—— (1934). *Arch. intern. Med.*, **53**, 792.
—— (1936). *Medical Papers Dedicated to Henry Asbury Christian*. Waverly Press.
—— and Goldshine, A. D. (1940). *Amer. J. med. Sci.*, **200**, 465.
—— and Pratt, J. H. (1931). *Arch intern. Med.*, **47**, 675.
Barach, J. H. (1928). *J. Amer. med. Ass.*, **91**, 1511.
Bauman, L. (1928). Ibid., **90**, 22.
Bell, E. T., and Clawson, B. J. (1928). *Arch. Path.*, **5**, 939.
Benedict, F. G. (1915). *A Study of Prolonged Fasting*. Carnegie Institution of Washington.
—— Miles, W. R., Roth, P., and Smith, H. M. (1919). *Human Vitality and Efficiency under Prolonged Restricted Diet*. Carnegie Institution of Washington Publication, No. 280.
Bickel, H. (1914). *Neurol. Zbl.*, **33**, 90. Cited by Fishberg (1939), p. 602.
Binger, C. (1945). *Bull. N.Y. Acad. Med.*, **21**, 610.
Blalock, A., and Levy, S. E. (1937). *Ann. Surg.*, **106**, 826.
Bramwell, J. C. (1924). *Quart. J. Med.*, **17**, 225.
Braun-Menéndez, E., Fasciolo, J. C., Leloir, L. F., Munoz, J. M., and Taquini, A. C. (1946). *Renal Hypertension*. Thomas, Springfield, Illinois.
Brooks, H., and Carroll, J. H. (1912). *Arch. intern. Med.*, **10**, 97.
Brown, G. E. (1929–30). *Ann. intern. Med.*, **3**, 1177.
Bruce, M. B., Martin, R. T., and Smirk, F. H. (1945). *J. Physiol.*, **103**, 412.
Cadbury, W. W. (1922). *Arch. intern. Med.*, **30**, 362.
—— (1923). *China med. J.*, **37**, 823. Cited by Krakower (1933–4).
Campbell, H. E., and Blankenhorn, M. A. (1925–6). *Amer. Heart J.*, **1**, 151.
Castleman, B., and Smithwick, R. H. (1943). *J. Amer. med. Ass.*, **121**, 1256.

Concepción, I., and Bulatao, E. (1916). *Philipp. J. Sci.*, Sec. B., **11**, 135.
Cox, A. J., jun., and Dock, W. (1941). *J. exp. Med.*, **74**, 167.
Cruickshank, E. W. H. (1923). *China med. J.*, **37**, 1. Cited by Krakower (1933–4).
Daley, R. M., Ungerleider, H. E., and Gubner, R. S. (1943). *J. Amer. med. Ass.*, **121**, 383.
Dieckmann, W. J., and Michel, H. L. (1935). *Arch. intern. Med.*, **55**, 420.
Diehl, H. S., and Hesdorffer, M. B. (1933). Ibid., **52**, 948.
Donnison, C. P. (1929). *Lancet*, **1**, 6.
Dublin, L. I., Fisk, E. L., and Kopf, E. W. (1925). *Amer. J. med. Sci.*, **170**, 576.
Dunbar, F. (1935). *Emotions and Bodily Changes*. Columbia Univ. Press, N.Y.
Ehrström, M. C. (1945). *Acta med. scand.*, **122**, 546.
Fahr, G., Davis, J., Kerkhof, A., Hallock, P., and Giere, E. (1932). *Amer. J. Physiol.*, **101**, 376.
Fahr, T. (1922). *Virchows Arch.*, **239**, 41.
Fahrenkamp, Karl (1926). Die psycho-physischen Wechselwirkungen bei den Hypertonie-Erkrankungen. Eine klinische Studie über die praktische Bedeutung der Blutdruckkurve. Hippokrates-verlag, Stuttgart. Cited by Dunbar (1935).
Farris, E. J., Yeakel, E. H., and Medoff, H. S. (1945). *Amer. J. Physiol.*, **144**, 331.
Fasciolo, J. C., Houssay, B. A., and Taquini, A. C. (1938). *J. Physiol.*, **94**, 281.
Feldt, R. H., and Wenstrand, D. E. W. (1942). *Amer. Heart J.*, **23**, 766.
Fischer, R. (1930). *Med. Klinik*, **26**, 625. Cited by Fishberg (1939), p. 602.
Fishberg, A. M. (1925). *Arch. intern. Med.*, **35**, 650.
—— (1939). *Hypertension and Nephritis*, 4th ed., p. 235. Lea and Febiger, Philadelphia.
Flaxman, N. (1934). *Amer. J. med. Sci.*, **188**, 639.
Fleming, W. D. (1924). *J. metab. Res.*, **6**, 87. Cited by Shattuck (1933).
Foster, J. H. (1927). *Arch. intern. Med.*, **40**, 38.
—— (1930). *New. Engl. J. Med.*, **203**, 1073.
Fraser, J., and Cowell, E. M. (1918). *J. Amer. med. Ass.*, **70**, 520.
Friedlander, A. (1927). *Medicine*, **6**, 143.
Frost, H. M. (1926). *Life Insurance Med.*, Boston, **1**, 178.
Gager, L. T. (1930). *Hypertension*, p. 329. Williams and Wilkins Co., Baltimore.
Garreton-Silva, A., Rodríguez, A., and Aspillaga, A. (1941). *Rev. méd. Chile*, **69**, 629. Cited by Braun-Menéndez *et al.* (1946), p. 282.
Gates, R. G. (1946). *Human Genetics*. Macmillan Co., N.Y.
Gelshtein, E. M. (1943). *Klin. Med.*, **21**, 12, 10. Cited by A. Ruskin, *Amer. Rev. Soviet Med.*, 1946, **3**, 260.
Gillespie, R. D. (1924). *J. Physiol.*, **58**, 425.
Glomset, D. J. (1931). *J. Iowa med. Soc.*, **21**, 220.
Goldblatt, H. (1947). *Physiol. Rev.*, **27**, 120.
—— and Kahn, J. R. (1940). *Studies on Experimental Hypertension* XIII, p. 266. Science Press, Washington.
—— Lynch, J., Hanzal, R. F., and Summerville, W. W. (1934). *J. exp. Med.*, **59**, 347.
Goldring, W., Chasis, H., Ranges, H. A., and Smith, H. W. (1941). *J. clin. Invest.*, **20**, 637.
Graham, A. W., Hines, E. A., and Gage, R. P. (1945). *Amer. J. Dis. Child.*, **69**, 203.
Graham, J. D. P. (1945). *Lancet*, **1**, 239.
Graybiel, A., Allen, A. W., and White, P. D. (1935). *J. clin. Invest.*, **14** 52
Grollman, Arthur (1929). *Amer. J. Physiol.*, **89**, 584.
Grollman, A. (1944). Ibid., **142**, 666.
—— Harrison, T. R., and Williams, J. R. (1943). Ibid., **139**, 293.
Gubner, R., Silverstone, F., and Ungerleider, H. E. (1946). *J. Amer. med. Ass.*, **130**, 325.
Hall, S. B. (1927). *Lancet*, **2**, 540
Hamperl, H., and Heller, H. (1934). *Arch. exp. Path. Pharmak.*, **174**, 517.
Hartman, H. R., and Ghrist, D. G. (1929). *Arch. intern. Med.*, **44**, 877.
Hashimoto, H., Akatsuka, K., Tsujii, I., and Shiraishi, H. (1933–4). *Ann. intern. Med.*, **7**, 615.
Hedley, O. F. (1941). *Publ. Hlth Bull., Wash.*, No. 268. Cited in *Bull. Hyg.*, 1942, **17**, 553.
Heimann, H. L., Strachan, A. S., and Heyman, S. C. (1929). *British Medical Journal*, **1**, 344.
Heyer, H. E., and Keeton, R. W. (1941). *Amer. J. clin. Path.*, **11**, 818.
Hill, L. (1898). *J. Physiol.*, **22**, xxvi.
Hines, E. A., jun. (1937–8). *Ann. intern. Med.*, **11**, 593.
—— (1940). *J. Amer. med. Ass.*, **115**, 271.
—— and Brown, G. E. (1935). *Proc. Mayo Clin.*, **10**, 371.
Holmes, S. J. (1931). *Hum. Biol.*, **3**, 203.
Houssay, B. A., and Fasciolo, J. C. (1937). *Rev. Soc. argent. Biol.*, **13**, 284.
Houston, W. R. (1929). *Med. Clin. N. Amer.*, **12**, 1285.
Huber, E. G. (1927). *J. Amer. med. Ass.*, **88**, 1554.
Hueper, W. C. (1944). *Arch. Path.*, **38**, 245.
Hunter, A. (1939). *J. Inst. Actuaries*, **70**, 60. Cited by Daley *et al.* (1943).
Ismail, Abd-El-Aziz (1928). *Lancet*, **2**, 275.
Katz, L. N., Mendlowitz, M., and Friedman, M. (1938). *Proc. Soc. exp. Biol., N.Y.*, **37**, 722.
Kean, B. H. (1941). *Arch. intern. Med.*, **68**, 466.
—— (1944). *Amer. J. trop. Med.*, **24**, 341. Cited by Taylor (1945).
Kerley, C. G., and Lorenze, E. J. (1942). *J. Paediat.*, **20**, 383.
Kilborn, L. G. (1926). *China med. J.*, **40**, 1. Cited by Krakower (1933–4).
Kilpatrick, J. A. (1948). *Brit. Heart J.*, **10**, 48.
Kimmelstiel, P. (1933). *Virchows Arch.*, **290**, 245.
Kirk, E. J. (1931). *J. industr. Hyg.*, **13**, 314.
Krakower, A. (1933–4). *Amer. Heart J.*, **9**, 396.
Klemola, Erkki (1938). *Z. KonstLehre*, **22**, 69. Cited by Gates (1946), p. 932.
Kronfeld, A. (1932). Kreislaufneurosen bezw. Herzneurosen vom standpunkt des Psychotherapeuten. In *Herzneurosen und Modern Kreislauftherapie*, Steinkopff, Dresden und Leipzig, 18. Cited by Dunbar (1935).
Lantin, G. T. (1933). *J. Philipp. med. Ass.*, **13**, 191.
Laws, C. L. (1932–3). *Amer. Heart J.*, **8**, 608.
Levy, R. L., Hillman, C. C., Stroud, W. D., and White, P. D. (1944). *J. Amer. med. Ass.*, **126**, 829.
—— White, P. D., Stroud, W. D., and Hillman, C. C. (1945a). Ibid., **128**, 1059.
—— —— —— —— (1945b). Ibid., **129**, 585.
McCay, D. (1907). *Lancet*, **1**, 1483.
—— (1908). *Sci. Mem. Govt India*, **34**, 23.
McGeorge, M. (1945). *Quart. J. Med.*, n.s. **14**, 171.
MacKenzie, L. F., and Shepherd, P. (1937). *Proc. Ass. Life Insur. med. Dir. Amer.*, **24**, 157. Cited by Levy *et al.* (1945a).
MacWilliam, J. A. (1923). *British Medical Journal*, **2**, 1196.
—— (1925). *Physiol. Rev.*, **5**, 303.
Master, A. M. (1943). *Bull. N.Y. Acad. Med.*, **19**, 704.
—— and Oppenheimer, E. T. (1929). *J. Amer. med. Ass.*, **92**, 1652.
Medoff, H. S., and Bongiovanni, A. M. (1945). *Amer. J. Physiol.*, **143**, 297.
Menninger, K. A. (1938). *Bull. N.Y. Acad. Med.*, **14**, 198.
Moller, E. (1931). *Acta med. scand.*, **74**, 341.
von Monakow, P. (1920). *Dtsch. Arch. klin. Med.*, **133**, 129.
Moritz, A. R., and Oldt, M. R. (1937). *Amer. J. Path.*, **13**, 679.
Moschcowitz, E. (1919). *Amer. J. med. Sci.*, **158**, 668.
—— (1945). *J. Mt Sinai Hosp.*, **11**, 357.
Mueller, O. (1922). *Die Kapillaren der menschlichen Koerperflaeche*, p. 118. Stuttgart.
Mueller, S. C., and Brown, G. E. (1930). *Ann. intern. Med.*, **3**, 1190.
Müller, C. (1921). *Acta med. scand.*, **55**, 381.
Nuzum, F. R., and Elliot, A. H. (1931). *Amer. J. med. Sci.*, **181**, 630.
Nye, L. J. J. (1937). *Med. J. Austral.*, **2**, 1000.
O'Hare, J. P., Walker, W. G., and Vickers, M. C. (1924). *J. Amer. med. Ass.*, **83**, 27.
Page, I. H., and Corcoran, A. C. (1945). *Arterial Hypertension: Its Diagnosis and Treatment*, p. 252. Year Book Publishers, Chicago.
Pal, J. (1919). *Med. Klinik*, **15**, 662. Cited by Braun-Menéndez *et al.* (1946), p. 282.
Palmer, R. S. (1930). *J. Amer. med. Ass.*, **94**, 694.
—— (1931). *New Engl. J. Med.*, **205**, 1233.
Patton, H. S., Page, E. W., and Ogden, E. (1943). *Surg. Gynec. Obstet.*, **76**, 493.
Pei-Lin, Li (1940). *J. Path. Bact.*, **50**, 121.
Perera, G. A., and Blood, D. W. (1947a). *Ann. intern. Med.*, **27**, 401.
—— —— (1947b). *J. clin. Invest.*, **26**, 1109.
—— Knowlton, A. I., Lowell, A., and Loeb, R. F. (1944). *J. Amer. med. Ass.*, **125**, 1030.
Pickering, G. W. (1945). *Clin. Sci.*, **5**, 229.
—— and Kissin, M. (1936). Ibid., **2**, 201.
—— —— and Rothschild, P. (1936). Ibid., **2**, 193.
Platt, R. (1947). *Quart. J. Med.*, n.s. **16**, 111.
—— (1948). Ibid., n.s. **17**, 83.
Preble, W. E. (1923). *Boston med. surg. J.*, **188**, 617.
Raghavan, P. (1941). *J. Indian med. Ass.*, **10**, 365. Cited in *Bull. Hyg.*, 1942, **17**, 33.
Robinson, S. C., and Brucer, M. (1939). *Arch. intern. Med.*, **64**, 409.
—— —— and Mass, J. (1940). *J. Lab. clin. Med.*, **25**, 807.
Rodbard, S., and Katz, L. N. (1939). *Amer. J. med. Sci.*, **198**, 602.
—— —— (1941). *J. exp. Med.*, **73**, 357.
Rogers, W. F., and Palmer, R. S. (1944). *New Engl. J. Med.*, **230**, 39.
Rony, H. R. (1940). *Obesity and Leanness*. Lea and Febiger, Philadelphia.
Rose, R. H. (1923). *Amer. Med.*, **18**, 418.
Ruskin, A., Beard, O. W., and Schaffer, R. L. (1948). *Amer. J. Med.*, **4**, 228.
Russek, H. I. (1943). *Amer. Heart J.*, **26**, 398.
—— and Zohman, B. L. (1945). Ibid., **29**, 113.
Russell, D. S. (1929). A Classification of Bright's Disease. Privy Council Med. Res. Coun. Sp. Rep. Ser., No. 142. London.
Salcedo, Juan, jun., and Pascual, Wenceslao (1932). *J. Philipp. med. Ass.*, **12**, 205.
Schultz, J. H. (1932). *Das autogene Training (konzentrative Selbstentspannung)*, p. 305. Thieme, Leipzig. Cited by Dunbar (1935).
Schultze, V. E., and Schwab, E. H. (1936). *Amer. Heart J.*, **11**, 66.
Scott, R. W. (1944). *Arch. Surg.*, **49**, 192.
Shattuck, G. C. (1930). *The African Republic of Liberia and the Belgian Congo*. Harvard Univ. Press, Cambridge. Cited by Schulze and Schwab (1936).
—— (1933). *The Peninsula of Yucatan; Medical, Biological, Meteorological, and Sociological Studies*. Carnegie Institution of Washington.
Shaw, A. F. B., and Ghareeb, A. A. (1938). *J. Path. Bact.*, **46**, 401.
Short, J. J., and Johnson, H. J. (1939). *Amer. J. med. Sci.*, **198**, 220.
Smirk, F. H. (1933–4). *Clin. Sci.*, **1**, 131.
—— (1934). *Proc. roy. Soc. Med.*, **27**, 1485.
—— (1944). *Brit. Heart J.*, **6**, 176.
—— (1947). *N.Z. med. J.*, **46**, 86.

Smithwick, R. H. (1944). *Arch. Surg.*, **49**, 180.
Stieglitz, E. J. (1930). *Amer. J. med. Sci.*, **179**, 775.
Stocks, P., and Karn, M. N. (1924). *Blood Pressure in Early Life*. Camb. Univ. Press.
Stone, C. T., and Vanzant, F. R. (1927). *J. Amer. med. Ass.*, **89**, 1473.
Symonds, B. (1923). Ibid., **80**, 232.
Terry, A. H. (1923). Ibid., **81**, 1283.
Tigerstedt, C. (1926). *Skand. Arch. Physiol.*, **48**, 138. Cited by Dunbar (1935).
Torgerson, W. R. (1929). *P.R. J. publ. Hlth*, **5**, 438.
Transactions of the International Congress on Life Assurance Medicine, London. 1935.
Tung, C. L. (1927). *Arch. intern. Med.*, **40**, 153.
—— (1928). *Chin. J. Physiol.*, **93**, 1. Cited by Krakower (1933–4).
—— (1930). Ibid., **4**, 117. Cited by Krakower (1933–4).
Verney, E. B., and Vogt, M. (1938). *Quart. J. exp. Physiol.*, **28**, 253.
—— —— (1943). Ibid., **32**, 35.
Volhard, F. (1931). In Mohr and Staehelin's *Handbuch der inneren Medizin*, 2nd ed., **6**, 508.
Wallgren, A. (1922). *Acta med. scand.*, **56**, 356.
Weiss, M. M., and Prusmack, J. J. (1938). *Amer. J. med. Sci.*, **195**, 510.
Weitz, W. (1923). *Z. klin. Med.*, **96**, 151.
—— and Sieben, A. (1926). *Münch. med. Wschr.*, **73**, 2197. Cited by Dunbar (1935).
Wiggers, C. J. (1938). *Amer. J. Physiol.*, **123**, 644.
Williams, A. W. (1944a). *E. Afr. med. J.*, **21**, 328.
—— (1944b). Ibid., **21**, 368.
Wilson, C., and Byrom, F. B. (1939). *Lancet*, **1**, 136.
—— —— (1941). *Quart. J. Med.*, n.s. **10**, 65.
—— and Pickering, G. W. (1937–8). *Clin. Sci.*, **3**, 343.
Wood, J. E., and Cash, J. R. (1939). *Ann. intern. Med.*, **13**, 81.
Yates, M. R., and Wood, J. E. (1936). *Proc. Soc. exp. Biol, N.Y.*, **34**, 560.
Ying, Y. Y. (1926). *China med. J.*, **40**, 641. Cited by Krakower (1933–4).

THE ROLE OF INFECTION IN GRANULOPENIA

BY

KENNETH ROBERTSON, M.D., F.R.C.P.

Physician, Royal Hants County Hospital, Winchester, and Royal South Hants Hospital, Southampton

In 1922 Schultz first reported a condition of severe and progressive oral sepsis associated with granulopenia, which often ended fatally. There can be no doubt that in the earlier cases the importance of sepsis was realized and stressed, but during the twenty years which followed Schultz's paper the aetiological emphasis shifted from infection to the leucotoxic drugs, the administration of which often coincided with the appearance of "malignant neutropenia," as this syndrome was now called.

Reports of cases associated with the taking of compounds containing amidopyrine began to appear on the Continent in 1930, and later in this country. The evidence against these drugs seemed irrefutable, particularly when it was shown that, in some patients who had recovered, a further small dose immediately produced a profound fall in the number of circulating granulocytes. With further experience other therapeutic agents fell under suspicion, and cases of dangerous neutropenia were reported after the use of organic arsenic, gold salts, sulphonamides, and, more recently, the thiouracils. This list is by no means complete, but is sufficient for the present purpose.

As familiarity with the condition increased, more and more importance was focused upon the leucotoxic agent, while the infection which invariably accompanied the condition came to be regarded as a purely secondary matter, due to invasion of the defenceless organism by bacteria. Thus Wilkinson (1936) uses such phrases as "the primary cause is clearly not bacteriological" and "it is apparently true, however, that the oral, throat, and other ulcerative or necrotic lesions are secondary to the blood condition, and not vice versa."

This view has undoubtedly held the field with little or no question, though all writers on the subject have referred to the fact that malignant neutropenia is from time to time encountered in certain severe infections, particularly staphylococcal septicaemia and osteomyelitis, pneumonia, and liver abscess, when none of the usually accepted leucotoxic drugs have been used. Witts (1936) points out that patients whose white cells have been depressed by one of these drugs may or may not develop the acute illness, depending upon chance exposure to infection. He also refers to animal experiments which seemed to show that such drugs make impossible the normal leucocyte response to infection.

Dameshek and Wolfson (1942) made a preliminary report on the treatment of agranulocytosis by sulphonamides. Nixon, Eckert, and Holmes (1943) described three cases in which agranulocytosis developed while infections were being attacked by sulphadiazine. Instead of withdrawing the drug, it was continued in larger doses, with the result that the blood pictures returned to normal and the patients recovered.

Since these papers, the part played by infection in granulopenic conditions has assumed increasing importance. There can be no doubt that many physicians have accepted Dameshek's advice regarding treatment and no longer worry about the blood picture, concentrating their efforts in overcoming the infection which is threatening to overwhelm the victim.

Boland, Headley, and Hench (1946) reported the cure of a case of total agranulocytosis following the use of gold—a particularly fatal combination—by means of penicillin. In the same paper they refer to fourteen other cases associated with various drugs successfully treated in the same way.

Nevertheless, Israëls (1948), writing of penicillin treatment, says: "Several cases have been reported in the literature, but the results are not very convincing. If there is evidence of sepsis, it is clear that penicillin should be given promptly." Acute agranulocytosis unassociated with sepsis must be exceedingly rare, though Hickie (1948) has described the case of a 70-year-old man whose blood appears to have been almost devoid of cells of the granular series for a period of three years, and in whom it seems that sepsis was infrequently seen, and only as mild superficial episodes.

In March, 1946, I had under my care a woman who developed a complete agranulocytosis while undergoing treatment with gold for rheumatoid arthritis. Two previous similar cases under my care had quickly ended fatally in spite of vigorous treatment, using all the recognized methods of bone-marrow stimulation. In this case penicillin was added to the treatment, and recovery was prompt and complete.

A Series of Cases

While serving on the Medical Division of a military hospital during 1947 I had the opportunity of treating a number of cases in which severe granulopenia complicated arsenical treatment of syphilis. In addition to N.A.B. all these cases were receiving bismuth, an agent which appears in the list of leucotoxic materials given by Beaumont and Dodds (1947), though I have been unable to discover the report of any case in which granulopenia followed the use of bismuth without arsenic.

In the earlier cases British anti-Lewisite (BAL), "pentide," blood transfusion, ascorbic acid, liver extract, and other bone-marrow stimulants were used in addition to penicillin. In six subsequent cases penicillin alone was employed, with very satisfactory results. McManus (1946) records a similar experience. A case of "arsenical agranulocytosis" treated with BAL and pentide failed to improve until penicillin was added to the treatment. In a second case cure was rapidly achieved by the use of penicillin alone.